DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Our STN: BL 125392/0

OMRIX Biopharmaceuticals, Ltd.
Attention: -------(b)(4)---------
--------(b)(4)--------

Dear --(b)(4)--:

This letter is in regard to your biologics license application (BLA) for Fibrin Pad, manufactured at your Rehovot, Nes-Ziona, Israel location, submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

We have completed our review of all the submissions you have made relating to this BLA. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

CMC:

1. Outstanding issues from the Pre-License Inspection (PLI) performed on May 10 through May 19, 2011 at ----------(b)(4)---------- and Fibrin Pad Production Facility and detailed on form FDA-483 are not resolved. Please submit documentation that demonstrates that all outstanding inspectional issues identified during the PLI have been corrected.

CLINICAL:

2. The review of the submitted data shows an unfavorable trend towards the investigational product (FP) with regards to thrombotic events (TEs). Specifically, our review identifies the following:

    a. In the non randomized part of the study 400-07-002, a total of nine TEs were reported in seven subjects of 51 subjects enrolled in the study. As the cluster of TEs were seen in the non-randomized, uncontrolled part of the study, it is not possible to draw a conclusion regarding the association of the investigational product with these AEs.

    b. Given the lack of sufficient detail regarding operative placement of all investigational products used per patient, it is difficult to conclude with any degree of certainty that the FP did not contribute to the thrombotic events.

    c. The safety data captured under Protocol 400-08-002 (non-IND study) do not adequately address FDA's concern with regards to the AEs seen in the 400-07-002

study because it is unclear if the patients were adequately monitored to capture the TEs.

d. Furthermore, it is unclear if the patients were adequately monitored to capture thromboembolic events, infections, abscesses, adhesions/ obstructions.

Therefore, in order to support licensure of Fibrin Pad for use as an adjunct to hemostasis in soft tissue surgery, please submit data from an additional adequate and well controlled study designed primarily to assess safety in the proposed population. The study should be designed to include a prospective monitoring plan for thrombotic events.

Alternatively, you may submit safety data from an adequate and well controlled study with the Fibrin Pad in an ongoing study in a different surgical population.

BIMO INSPECTIONS:

3. FDA inspections and monitoring reports reveal issues with regard to conduct of the trial.

   a. Please submit detailed information on how all the investigators and sub-investigators were trained to comply with the study requirements.

   b. Failure to prepare or maintain case histories with respect to observations and data pertinent to the investigation:

      The protocol required that certain Inclusion and Exclusion criteria be determined by the Clinical Investigator during surgery, where study specific procedures, such as randomization and the application of the study drug, are to be performed. Operation Reports for subjects 11104, 11106, 11108, 11109, 11113, 11114, 111115, and 11203, which constitute more than a third of the study subjects at this site, do not mention the use of the study drug during surgery, yet this data was submitted to the Sponsor, as stated in the Soft Tissue Study Worksheets (found in the subject's records) and in the data listings provided by the Sponsor. Please identify and submit the source of the missing information in the Operative Reports that were submitted to FDA.

   c. Failure to comply with 21 CFR 312.61: Study drug was administered to subjects not under the investigator's supervision or under the supervision of a sub-investigator responsible to the investigator. Specifically, the Operative Report for subject 11112, dictated by -----(b)(6)----- (not listed in the Statement of Investigator, Form FDA 1572), described the use of the study drug during the surgery but does not mention the Clinical Investigator or Sub-Investigator as being present at any point during the procedure. The Nurse Intraoperative Report also does not list the Clinical Investigator or Sub-Investigator as being present during the surgery. Please explain.
   d. An investigation was not conducted in accordance with the investigational plan. Specifically:

i. The protocol states that: "Prior to participation, the study procedures and any known or likely risks will be explained to the subjects by the investigator or other medically qualified co-investigator." In 4 of 18 instances, the study procedures and any known or likely risks were explained to potential subjects (who were eventually enrolled into the study) by Study Coordinators who also signed the Informed Consent Form, when the Clinical Investigator or Sub-Investigator were not available to do so. Except for a letter from the Sponsor dated March 10, 2011, provided to FDA during the inspection by Dr. Bochicchio, a Co-Investigator was not identified anywhere in the protocol as a Study Coordinator or any other study staff member. This letter stated that the term "medically qualified co-investigator" should have been edited as "or designee", yet this was not edited or reviewed and approved by the IRB. Study Coordinators listed in the "Delegation of Authority" for protocol 400-07-002, which was signed by Dr. Bochicchio, are not qualified to practice medicine. Please explain.

ii. There is no evidence that five members from the research study staff, listed in the "Delegation of Authority" as being Study Coordinators, authorized to obtain Informed Consent, complete Case Report Forms, obtain Medical History and conduct subject follow-up, were qualified and trained on the specifics of the protocol to do so. Please explain.

e. The "Site Initiation Training" attendance log, dated April 10, 2008, provided by ----------(b)(4)----------, at the University of Maryland Medical Center, does not list the following individuals as being present during the site initiation training, yet they are listed in the "Delegation of Authority" (Exhibit 3) for this study: -----(b)(6)-----, Sub-Investigator (attended protocol-specific training on 06/24/2008, but was not present at the site initiation); ---------(b)(6)----------, Study Coordinator; ---------(b)(6)--------, Study Coordinator; ---------(b)(6)--------, Study Coordinator; -------(b)(6)-------, Study Coordinator; and ------(b)(6)-------, Study Coordinator. Please submit all training documentations at this site. Also, please submit documentations to confirm that the above mentioned investigators underwent training.

f. Sixteen of thirty two subjects were enrolled in another investigational study while participating in Protocol 400-07-002 at University of Alabama, Birmingham, Alabama site and there was no documented evidence of sponsor and/or IRB notification and/or approval to enroll the subjects in concurrent studies. Please submit detailed information on the sponsor/IRB notification and subject consents to participate in another investigational study.

COMPARABILITY PROTOCOL (CP):

4. Regarding the validation of the revised manufacturing process for the Fibrin Pad with the introduction of an ----------(b)(4)----------, please provide the following specific details:

    a. ----------(b)(4)----------.

    b. ----------(b)(4)----------.

    c. ----------(b)(4)----------.

    d. ----------(b)(4)----------.

    e. ----------(b)(4)----------.

    f. ----------(b)(4)----------.

    g. ----------(b)(4)----------:

        i. ----------(b)(4)----------.

        ii. ----------(b)(4)----------.

5. Regarding Comparability Program for the Fibrin Pad Drug Product:

    a. Please include testing at refrigerated storage conditions -(b)(4)- in your stability program for the revised process and continue to use the ----------(b)(4)----------

test and the ----------(b)(4)---------- test until the shelf life is established. Please note that at least 6 months stability data should be submitted in a Prior Approval Supplement for these changes.

b. Please specify statistical methods you plan to use to compare the in-process, release, characterization, and stability data for Fibrin Pad batches manufactured with the revised and current processes. Please provide a definition for "similar" trends in stability indicating parameters.

c. ----------(b)(4)----------.

d. Please specify the length of the observation period, parameters to be monitored and pre-determined acceptance criteria in your studies of the functional performance of the Fibrin Pad (revised process) in the non-clinical model. Please note that the observation period should correlate with the period of Fibrin Pad resorption.

7. Please note that a list of all protocols, validation studies and documents that you intend to provide data for in the executed CP report, have to be included in the comparability protocol. In addition, all deviations and investigational reports generated during the execution of the CP should be submitted to FDA in the executed CP report.

8. As previously discussed with FDA, the data from the executed Comparability Protocol QA-P-FP-0017-00 for introduction of an ----------(b)(4)---------- should be submitted to FDA for review as a prior approval supplement following approval of the original BLA.

LABELING

9. We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling.

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; or (3) withdraw the application.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. For PDUFA products please submit your meeting request as described in our "Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products," dated February 2000. This document is available on the internet at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/U

CM079744.pdf or may be requested from the Office of Communication, Outreach, and Development, at (301) 827-1800. For non-PDUFA products, please contact the regulatory project manager. For details, please also follow the instructions described in CBER's SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants. This document also is available on the internet at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm, or may be requested from the Office of Communication, Outreach, and Development.

Please be advised that, as stated in 21 CFR 601.3(c), if we do not receive your complete response within one year of the date of this letter, we may consider your failure to resubmit to be a request to withdraw the application. Reasonable requests for an extension of time in which to resubmit will be granted. However, failure to resubmit the application within the extended time period may also be considered a request for withdrawal of the application.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Sonday Kelly, at (301) 827-6122.

Sincerely yours,

Basil Golding, M.D.
Director
Division of Hematology
Office of Blood Research and Review
Center for Biologics
Evaluation and Research